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META-ANALYSIS

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The efficacy and safety of patient-specific instrumentation in primary total knee replacement: a systematic review and meta-analysis

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ABSTRACT

Introduction: Patient-specific instrumentation (PSI) for primary total knee arthroplasty (TKA) surgery has been shown to increase accuracy of component positioning. However, it is unclear whether this also translates to actual benefits for patients in terms of better outcomes (efficacy) or less complications such as revisions (safety). We therefore systematically reviewed the literature to determine the efficacy and safety of PSI in primary TKA.

Methods: Randomized controlled trials comparing PSI to non-PSI in primary TKA were included. A random effects model was used with meta-regression in case of heterogeneity.

Results: Forty-three studies were included with a total of 1816 TKA in the PSI group and 1887 TKA in the control group. There were no clinically relevant differences between the PSI-group and non-PSI group regarding all outcomes. There was considerable heterogeneity: meta-regression analyses showed that the year the study was published was an important effect modifier. Early publications tended to show a positive effect for PSI compared to non-PSI TKA, whereas later studies found the opposite.

Conclusion: Based on evidence of moderate certainty, our study suggested that there were no clinically relevant differences in efficacy and safety between patients treated with PSI TKA and patients treated with non-PSI TKA.

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Total knee replacement; Patient-specific instrumentation; patient reported outcome measures; publication bias; revision surgery; kinematic alignment

1. Introduction

Patient-Specific Instrumentation (PSI) has been developed to improve alignment in total knee replacement (TKR) and has been suggested to improve surgical efficacy and to reduce complications because PSI does not require opening of the intramedullary canal [1,2]. There is ongoing debate whether routine use of PSI in primary TKR is justified or not: while there are some systematic reviews that argue in favor of PSI [1,3], there are also those that argue against the routine use of PSI [4]. Moreover, recent systematic reviews that comprehensively evaluate the efficacy and safety of PSI are lacking. Hence it is important to update our knowledge on both the efficacy and safety of PSI in primary TKR. We therefore systematically reviewed the literature to determine the efficacy and safety of patient-specific instrumentation in primary total knee replacement.

2. Methods

2.1. Study design

The reporting of this systematic review and meta-analysis was in accordance with the PRISMA-statement and a protocol has been registered prior to the start of the study at Open Science Forum (https://osf.io/nsqjy/?view_only=2d8153e8554b4772bd3e4d20739cda2d). The following PICOS question is the subject of this systematic review:

Patients: Patients with primary total knee arthroplasty (TKA)
Intervention group: TKA with patient-specific instrumentation (PSI group)
Control group: TKA without PSI (control group)
Outcomes: efficacy and safety (see below for specification)
Studies: Randomized controlled trials (RCT)
Efficacy:

The primary outcome was patient reported outcome measures (PROMS), for which a 10% difference in score will be considered to be minimally clinically relevant as defined prior to the start of the study [5]. The secondary outcomes for efficacy were clinical outcome scores such as the Knee Society Score (KSS) and Length of Stay (LOS).

Safety:

To assess safety, the following secondary outcomes were considered: peri-operative blood loss, blood transfusions, hematoma's, revision for any reason, revision for aseptic

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loosening, revision for infection, revision for instability, prosthetic joint infection (PJI), manipulation under anesthesia (MUA), fractures (articular or non-articular), total re-operations, total re-interventions, deep venous thrombosis (DVT), pulmonary embolism (PE), implant migration as measured with radio stereometric analysis (RSA), total complications.

2.2. Data sources and search strategy

A thorough literature search was performed together with a medical information specialist (JS). The following databases were searched from their inception up to July 2022: PubMed, Embase (OVID version), Web-of-Science, Cochrane Library, Emcare (OVID version) and Academic Search Premier. The search consisted of the following concepts, each defined by a combination of controlled vocabulary and free text terms: (1) Total Knee Arthroplasty, (2) Patient Specific Instrumentation, and (3) Randomized Controlled Trial. Full details regarding the search strategy are reported in the appendix.

2.3. Study selection

Two reviewers (JH and RP) independently screened titles and abstracts of the records identified by the literature search strategy. Both reviewers recorded their findings in an electronic database that was designed before the start of the screening. These databases were compared, and any disagreement was resolved by consensus or by consulting a referee (BP). The same reviewers also independently evaluated the full-text papers of eligible studies against the inclusion and exclusion criteria. Any disagreement was resolved by consensus or by consulting the referee. The inclusion criteria were: (1) RCT, (2) primary TKA, (3) comparing PSI to non-PSI. The exclusion criteria were: 1) Not a RCT, (2) Not primary TKA (e.g. revision TKA, unicompartmental knee arthroplasty (UKA) or patellofemoral TKA), (3) not comparing PSI with non-PSI, (4) Language not spoken by the reviewer team, (5) no extractable data on outcomes for each group.

2.4. Data extraction and quality assessment

The two reviewers (JH and RP) independently extracted data and appraised the risk of bias from included studies regarding the outcome of interest, patient demographic details, and study characteristics in a predefined electronic datasheet. These datasheets were compared, and any disagreement was resolved by consensus or by consulting a referee (BP).

Risk of bias was appraised by the Cochrane Risk of Bias Tool 2 (ROB2) [6]. To assess the certainty of the evidence, we followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) recommendation [7].

2.5. Data synthesis and analysis

A random-effects model was used with DerSimonian-Laird's method for the meta-analysis in order to pool risk differences (RD) and mean differences (MD), so that an estimate of the overall RD (absolute RD) and overall MD with their corresponding 95% confidence intervals (CIs) could be calculated [8,9]. The RD was used, because it is an appropriate solution for the (expected) empty cell problem and it allows for calculation of the number needed to treat (NNT) [10,11].

The amount of statistical heterogeneity was assessed through visual inspection of the forest plots and by calculating I2 statistics [12]. In case I2 is 40% or more sub-group analyses or meta-regression was used to explore possible sources [12]. A-priori determined possible effect modifiers are the variables mentioned under data-extraction and study protocol (study characteristics, demographics, intervention details, control group details).

A funnel plot was constructed for studies reporting the primary outcome in order to estimate the amount of publication bias [12]. In case the funnel plot was asymmetric a trim-and-fill method was used to explore the direction and magnitude of the possible publication bias [12,13]. All analyses were performed with the metafor package in R statistics [13].

3. Results

3.1. Study selection and study characteristics

The search retrieved 1032 hits, of which 389 were unique deduplication. After selection 43 studies were included, with a total of 1816 TKA in the PSI group and 1887 TKA in the control group [14–56]. A flowchart of the study selection is shown in Figure 1. The dataset with details for each study can be found at open science forum (https://osf.io/nsqjy/?view_only=2d8153e8554b4772bd3e4d20739cda2d).

The study size ranged from 15 to 200 patients. From the included studies 22 were from Europe, 10 from Asia, 8 from North America, 2 from Oceania, and 1 from a consortium of Europe and North America. The included studies had a follow-up up to 5 years. In 61% of studies the PSI was MRI-based, and in 39% PSI was CT-based.

3.2. Risk of bias

The risk-of-bias for individual studies can be found at open science forum (https://osf.io/nsqjy/?view_only=2d8153e8554b4772bd3e4d20739cda2d). There were 26 studies with high risk of bias and 17 studies with some concerns. The high risk of bias was caused by problems with allocation concealment and blinding due to differences in pre-operative imaging between the groups: the PSI group required pre-operative CT scans or MRI scans in order to construct the PSI jigs, whereas the non-PSI group did not require these scans, so they were not obtained. Hence the patients and caregivers were aware of the allocation prior to surgery, so allocation concealment and blinding were compromised. Some studies adequately addressed this issue by also performing pre-operative scans in the non-PSI groups. However, these studies suffered from minor issues leading to some concerns.

Synthesis of the results and analyses

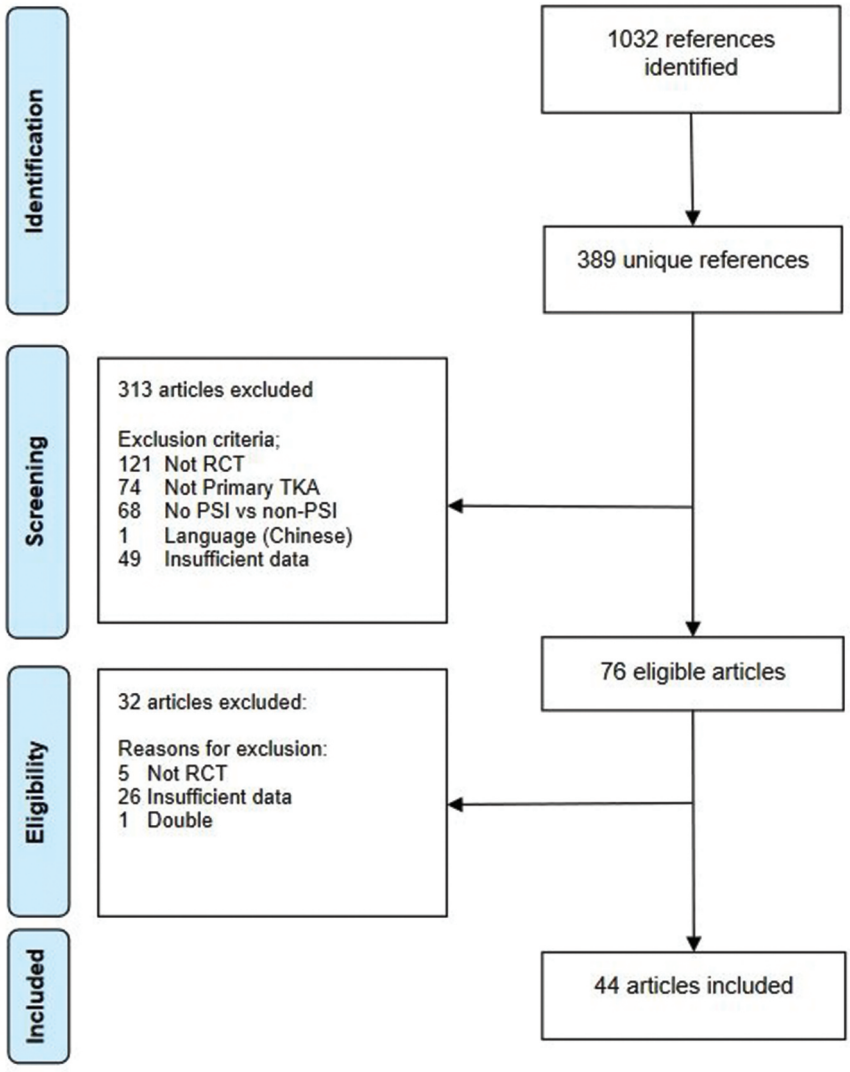

Figure 1. Prisma flow chart.

3.3. Patient reported outcome measures

A summary of the data-synthesis for PROMS is presented in Table 1. The primary outcome PROMS was measured as Oxford Knee Score in 12 studies, WOMAC score in 13 studies, EQ5D in 5 studies, SF12 in 3 studies and VAS pain in 8 studies. For all PROMS the pooled estimates and the 95% confidence intervals indicated that there were no clinically relevant difference between patients treated with PSI TKA and patients treated with non-PSI TKA; see Table 1 and Figure 2. There was, however, considerable heterogeneity of e.g. 51% for the OKS and 88% for the WOMAC, so a meta-regression analysis was warranted. The meta-regression analyses showed that this heterogeneity could be largely explained by the year the study was published; see Figure 3. Early publications tended to show a positive effect for PSI compared to non-PSI TKA, whereas later studies found the opposite.

3.4. Clinical outcome scores and length of stay

The secondary outcomes of Clinical Outcomes Scores were measured as Knee Society Score (KSS) in 22 studies, Hospital of Special Surgery Score (HSS) in 2 studies, Range of Motion (ROM) in 12 studies and Length of Stay (LOS) in 18 studies. For all Clinical Outcome Scores and LOS the pooled estimates and the 95% confidence intervals indicated that there were no clinically relevant differences between patients treated with PSI TKA and patients treated with non-PSI TKA; see Table 1. Except for HSS, the heterogeneity was less than 40% for these outcomes, so a meta-regression was not necessary. HSS, although showing 41% heterogeneity, was reported in only two studies, so a meta-regression was not appropriate.

3.5. Safety

A summary of the data-synthesis for safety is presented in Table 1. In the PSI group there was 66 ml [CI 31 ml to 101 ml] less blood loss compared to the non-PSI group. This difference was, however, not clinically relevant as it did not result in fewer blood transfusions; risk difference −0.5% [CI −2.2% to 1.3%]. There was no clinically relevant difference in the risk

Table 1. Summary of data synthesis.

	Outcome	Number of studies	Number of TKA	Pooled RD [CI]	Pooled mean difference [CI]	Heterogeneity (I^2)	GRADE
Efficacy	OKS	12	1133		0.2 [−1.1 to 1.4]	51%	M
	WOMAC	13	1417		0.9 [−1.9 to 3.8]	88%	M
	EQ5D	5	682		0.00 [−0.02 to 0.02]	0%	M
	SF12	3	223		1.0 [−2.5 to 4.5]	39%	M
	VAS pain	8	830		−3.1 [−7.2 to 1.0]	73%	M
	KSS	22	1945		0.7 [−0.3 to 1.7]	0%	M
	HSS	2	211		−0.6 [−3.2 to 2.0]	41%	M
	ROM	12	984		1.5 [−0.4 to 3.4]	36%	M
	LOS	18	1536		−0.3 [−0.4 to −0.1]	5%	M
Safety	Blood loss	20	1473		−66 [−101 to −31]	94%	M
	Blood transfusion	11	987	−0.5% [−2.2% to 1.3%		0%	M
	Hematoma	6	544	−0.0% [−2.7% to 2.6%]		9%	M
	Revision any reason	21	1992	−0.2% [−1.2% to 0.8%]		0%	M
	Revision aseptic loosening	20	1812	−0.2% [−1.1% to 0.7%]		0%	M
	Revision infection	20	1812	0.1% [−0.8% to 1.0%]		0%	M
	Revision instability	20	1812	0.1% [−0.9% to 1.0%]		0%	M
	MUA	18	1703	0.2% [−0.8% to 1.3%]		0%	M
	Fractures	18	1703	−0.1% [−0.9% to 0.8%]		0%	M
	Total reoperations	18	1703	−0.6% [−1.9% to 0.6%]		0%	M
	Total reinterventions	18	1703	−0.3% [−1.7% to 1.1%]		0%	M
	DVT/PE	10	1109	0.5% [−0.8% to 1.8%]		0%	M
	PE	7	856	0.4% [−1.1% to 1.8%]		0%	M
	Total complications	26	1591	0.2% [−1.2% to 1.7%]		0%	M
	MTPM	3	119		−0.03 [−0.14 to 0.09]	20%	M-H

RD = Risk Difference defined as risk PSI − risk non-PSI. Mean difference is defined as mean PSI − mean non-PSI. CI = 95% confidence interval. M = moderate certainty, M-H is moderate to high certainty

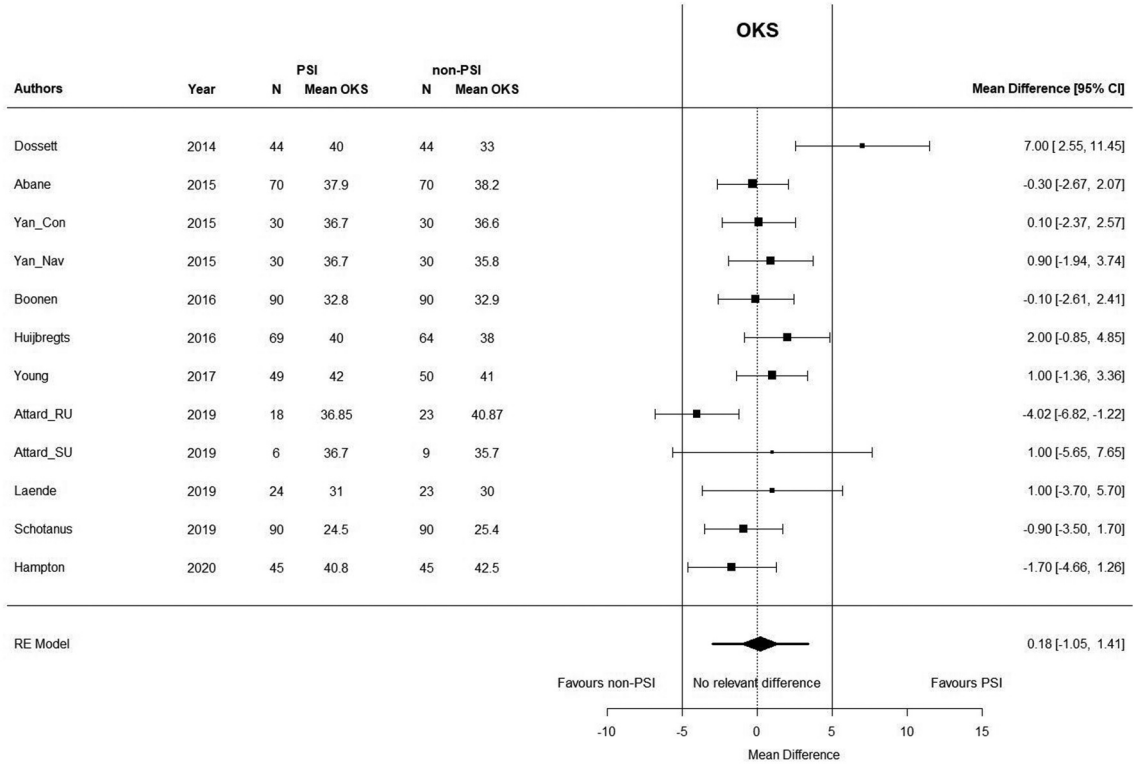

Figure 2. Forest plot showing the mean difference in Oxford Knee Score (OKS) between patients treated with PSI TKA and patients with non-PSI TKA. The pooled 95% confidence interval and 95% prediction interval were calculated with at random effects (RE) model.
Yan_Con is conventional TKA compared to PSI TKA form Yan et al.Yan_Nav is navigation (non-PSI) TKA compared to PSI TKA from Yan et al.Attard_RU is Reusable PSI TKA compared to Reusable non-PSI TKA from Attard et al.Attard_SU is Single use PSI TKA compared to Single use non-PSI TKA from Attard et al.

of hematoma, revision for any reason, revision for aseptic loosening, revision for infection, revision for instability, manipulation under anesthesia, fractures, total reoperations, total reinterventions, DVT/PE, PE or total complications. It is of note that there were 6 cases of DVT/PE in the PSI group (6 out of 558 patients) compared to 2 cases of DVT/PE in the non-PSI group (2 out of 551 patients), although the number of cases was too small to make any definite conclusions.

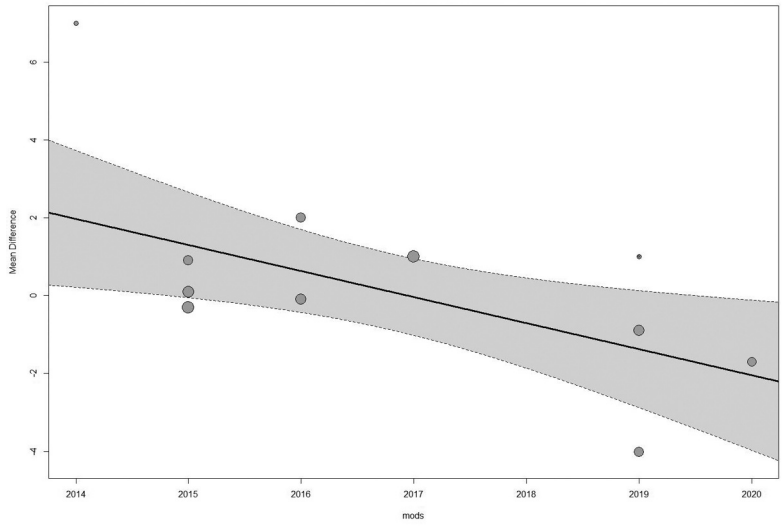

Figure 3. Graph showing the results from the meta-regression on mean difference of the Oxford Knee Score (OKS) according to the year the study was published. The size of the dots is inversely proportional to the variance of the estimated treatment effect, and the shaded area represents the 95% confidence interval. Early publications tended to show a positive effect for PSI compared to non-PSI TKA, whereas later studies found the opposite.

There was no clinically relevant difference in early migration (Maximal Total Point Motion (MTPM) at 12 months) as measured with RSA: mean difference of 0.03 mm [CI −0.09 mm to 0.14 mm] in favor of the PSI group.

3.6. Publication bias

The funnel plot (Figure 4) was asymmetric, suggesting publication bias in favor of the PSI group. This observation was confirmed by the trim-and-fill analyses which suggested 3 studies were missing (i.e. not published) that favored the non-PSI group: mean difference in OKS was −0.51 [CI −1.9 to 0.9] after correction for possible publication bias compared to 0.2 [CI −1.1 to 1.4] without correction for possible publication bias, so the possible influence of publication bias was considered to be small.

4. Discussion

4.1. Summary and general interpretation

In this systematic review and meta-analysis, we determined the efficacy and safety of patient-specific instrumentation in primary total knee replacement. The results of our study suggest that there were no clinically relevant differences in efficacy or safety for patients treated with PSI TKA or patients treated with non-PSI TKA. While there was 66 ml less blood loss in the PSI group compared to the non-PSI group, this difference was probably not clinically relevant as it did not result in fewer blood transfusions in the PSI group compared to the non-PSI group. There were 6 cases of DVT/PE in the PSI group (6 out of 558 patients) compared to 2 cases of DVT/PE in the non-PSI group (2 out of 551 patients). This finding is remarkable, but the number of cases was too small to make

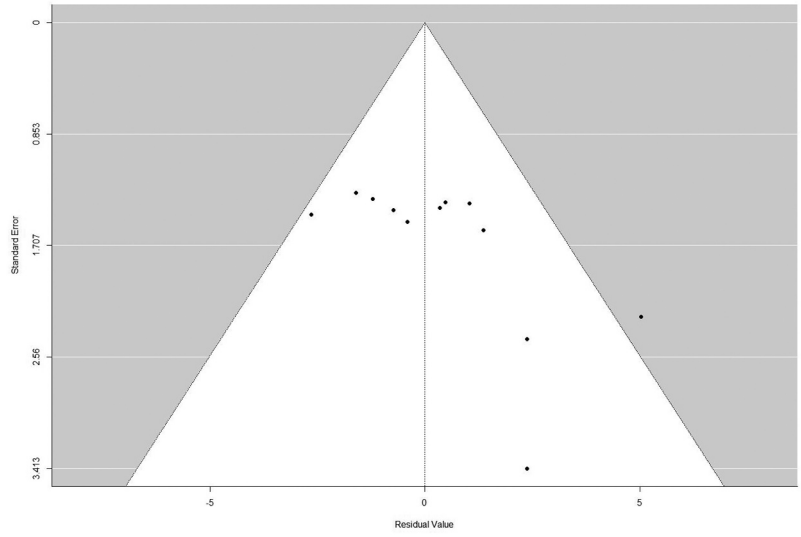

Figure 4. Funnel plot for Oxford Knee Score (OKS) when corrected for publication year. The funnel plot is asymmetric suggestion publication bias in favor of PSI TKA.

any definite conclusions and only 10 of 43 RCTs reported whether DVT/PEs occurred or not. It is thus important that orthopedic RCTs also consider and report general adverse events.

There were no clinically relevant differences in PROMS measured as OKS, WOMAC, EQ5D, SF12, and VAS Pain. There was considerably heterogeneity, so exploration of possible causes of this heterogeneity with meta-regression was indicated. The meta-regression showed that the heterogeneity could be largely explained by publication year. The studies that were published first (longest time ago) showed better PROMS for the PSI group compared to the non-PSI groups, whereas studies that were published more recently showed no difference or even better results with for the non-PSI group. We have also found evidence for publication bias in favor of the PSI-group, meaning that the pooled effects for PROMS are actually (slightly) worse for the PSI groups than calculated. Despite the heterogeneity and publication bias there was no clinically relevant difference in PROMS.

There were no clinically relevant differences in pooled revision rate between patients treated with PSI TKA and patients treated with non-PSI TKA based on 22 RCTs with a maximum of 5-year follow-up. There were 3 RSA studies measuring early migration (MTPM at 12 months) of tibial components relative to the tibial bone. Based on these 3 RSA studies, there was no difference in pooled early migration between the PSI components and the non-PSI components. Importantly, the confidence interval did not exceed the clinically relevant migration value of 0.2 mm [57,58]. Since early migration has been associated with long-term revision rate it is therefore expected that the long-term revision rates for aseptic loosening will not be clinically relevant different between PSI TKA and non-PSI TKA [57,59].

Recent reviews comparing PSI with non-PSI TKA have focused on accuracy of component positioning and axial alignment and have found favorable results for PSI [1,2]. Although these results are promising, one may ask whether this potential improved accuracy of component positioning also translates to actual benefits for patients in terms of better outcomes (efficacy) or less complications such as revisions (safety). The results of our systematic review suggest that this is not the case: there were no clinically relevant differences between the PSI and non-PSI groups.

4.2. Limitations and strengths

We acknowledge the following limitations. Firstly, the number of studies reporting on general adverse events such as DVT/PE were relatively limited. As a result there were only 8 cases of DVT/PEs in the entire meta-analysis, so the results may change when more cases are included in future analyses. Secondly, the follow-up of the included studies was limited to 5 years, so studies with long-term results were lacking. Although this is partially covered by the RSA studies which can predict long-term revision rates for aseptic loosening, it remains unclear how long-term revision rates for other reasons than aseptic loosening will be for patients with PSI TKR compared to patients with non-PSI TKR. Thirdly, the majority of included RCTs suffered from a high risk of bias. For most of these studies the allocation concealment and blinding were compromised: the PSI group required and received pre-operative CT scans or MRI scans to fabricate the PSI jigs, whereas the non-PSI group did not require or receive such scans. Nevertheless, for most outcomes the results of studies were very consistent with low heterogeneity giving confidence in the pooled results. For the outcomes with high heterogeneity, such as the OKS, the heterogeneity could be largely explained by publication year and the prediction interval was within the limits of what is considered clinically relevant, so this heterogeneity would not lead to different conclusions.

Our study has the following strengths. All phases of the review were performed in duplo by two reviewers. A protocol has been registered prior to the start of the review. The dataset underlying the analyses is available at an online data repository, so our results can be checked and future reviews may build on this dataset.

4.3. Conclusion

Based on evidence of moderate certainty, our systematic review and meta-analysis of 43 RCTs and 3.703 patients suggested that there were no clinically relevant differences in efficacy and safety between patients treated with PSI TKA and patients treated with non-PSI TKA.

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Declaration of interest

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Reviewers disclosure

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Data deposition

All data can be found at Open Science Forum: https://osf.io/nsqjy/?view_only=2d8153e8554b4772bd3e4d20739cda2d

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